Remarks

Claims 46-50, 55 and 57-86 are pending in the subject application and currently before the Examiner for consideration. Favorable consideration of the pending claims, in view of the remarks set forth herein, is respectfully requested.

Applicants gratefully acknowledge the Examiner's withdrawal of the rejection under 35 U.S.C. 112, second paragraph.

Claims 46-50, 55, 57-86 are rejected under 35 U.S.C. § 112, first paragraph, as nonenabled by the subject specification. Applicants respectfully traverse and assert that the claims as filed are enabled.

"To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). "That *some* experimentation may be required is not fatal; the issue is whether the amount of experimentation required is 'undue.'" *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Some experimentation, even a considerable amount, is not 'undue' if, for example, the specification provides a reasonable amount of guidance as to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

The Office Action indicates that the previously filed response was considered, but not found persuasive. Particularly, the Office Action argues that "the specification fails to teach that administered fragments and/or mutants of full length INSP035 (i.e., SEQ ID NOs: 5 and 7) treat lung fibrosis or liver fibrosis *in vivo*" (see Office Action at paragraph 1, page 5) and the "specification fails to characterize the active domains in the proteins which are critical to the claimed activity (i.e. anti-fibrotic activity). The specification fails to teach the *in vivo* administration of SEQ ID NOs: 5 and 7. The Examiner provided art which demonstrates that just because a variant protein has activity in an in vitro assay does not necessarily mean that variant will have the same activity *in vivo*" (Office Action, paragraph bridging pages 6-7).

With respect to the argument that "the specification fails to characterize the active domains in the proteins which are critical to the claimed activity", it is noted that Example 2 shows that SEQ ID NO:2 and a pair of fragments/mutants of SEQ ID NO: 2 (SEQ ID NOs:5 and 7) are capable of

inhibiting TRAIL. As shown in the attached alignment, SEQ ID NOs: 5 and 7 differ only by the first amino acid residue and fully align with the amino acid sequence spanning residues Asp(77) to Cys(163) of SEQ ID NO: 2. Thus, the as-filed specification does provide evidence and teaching as to the domains of the polypeptides associated with the claimed activity (*i.e.*, on the basis of the as-filed specification, the domain within INSP035 associated with TRAIL inhibiting activity is located between amino acid residues Asp(77) and Cys(163) of SEQ ID NO: 2, said amino acid residues being found in each of the claimed sequences (SEQ ID NOs: 2, 5 and 7)). Therefore, it is clear that the specification does provide information regarding the active domain in INSP035, that is important to the claimed activity and the claims recite polypeptides containing these domains.

It is also argued that the "specification fails to teach the *in vivo* administration of SEQ ID NOs: 5 and 7". While it is agreed that Example 5 is directed to the study of the *in vivo* effect of the long form of INSP035 (SEQ ID NO: 2), Applicants respectfully submit that: a) Example 5 teaches that "INSP035 administration in vivo protects against bleomycin induced lung fibrosis in mice", b) the term "INSP035" encompasses not only a polypeptide of SEQ ID NO: 2 but also a polypeptide of SEQ ID NO: 5 or 7 (see the specification on page 11, lines 26-34), and c) the polypeptides of SEQ ID NOs: 5 and 7 are specific fragments/mutants of SEQ ID NO: 2 that have been tested, *in vitro*, for activity and both SEQ ID NO: 5 and 7 have been shown to display similar activity, as compared to SEQ ID NO: 2, with respect to TRAIL inhibition *in vitro* (see Example 2). Thus, one skilled in the art would have reasonably concluded that both SEQ ID NOs: 5 and 7 would have similar bioactivity, in vivo, as compared to SEQ ID NO: 2.

Finally, the Office Action argues that the "Examiner provided art which demonstrates that just because a variant protein has activity in an *in vitro* assay does not necessarily mean that variant will have the same activity *in vivo*". While such a statement may be accurate, it is also accurate to state that just because an *in vivo* activity is not shown for a variant protein, it does not necessarily mean that the variant will not have the same activity as the parent protein *in vivo* (*i.e.*, it is also possible that the variant protein has the same activity as the original protein and the Office Action, at page 5, admits that this is recognized in the art). As argued in the previous response, active proteins and variants thereof having similar activities both *in vitro* and *in vivo* were known *(e.g.* PTH/PTH fragment and leptin/leptin fragments). This aspect has been further acknowledged by the Examiner

when citing Grasso (1997), a reference further demonstrating that short specific fragments of leptin are still active *in vivo* (see abstract). Such facts are relevant to the claimed polypeptides in that SEQ ID NOs: 5 and 7 are shorter fragments of SEQ ID NO: 2 (as noted above) and both SEQ ID NOs: 5 and 7 demonstrate similar activity to SEQ ID NO: 2 when assayed in vitro for the ability to inhibit TRAIL.

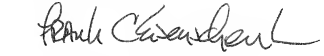
While the Office Action acknowledges at page 5 "that the art recognizes that shorter peptides (variants/mutants) can retain both *in vivo* and *in vitro* activity", it is also argued that "the specification fails to teach that *administered* fragments and/or mutants of full length INSP035 SEQ ID NO:2 (*i.e.*, SEQ ID NOs:5 and 7) treat lung fibrosis or liver fibrosis *in vivo*" (emphasis in the original). Essentially, the Examiner argues that the description and examples provided in the specification do not provide evidence of biological activity for the claimed polypeptides *in vivo*. To the extent that the rejection of record is based on the lack of working examples with respect to SEQ ID NOs: 5 and 7, Applicants note that compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed (see M.P.E.P. §2164.02). Applicants also note that the Court of Appeals for the Federal Circuit has held that it is improper to confuse "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption." *In re Brana*, 51 F.3d 1560, 1567 (Fed. Cir. 1995). Particularly, the *Brana* court held that "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." *Id.* at 1568. (The court's reference to "usefulness" was in the context of the how-to-use prong of 35 U.S.C. § 112, first paragraph; the rejection on appeal was for nonenablement. *See id.* at 1564). Furthermore, Applicants respectfully submit that one skilled in the art would have reasonably expected the claimed fragments of SEQ ID NO: 2 (*i.e.*, SEQ ID NOs: 5 and 7) to have the same activity *in vivo* as that of SEQ ID NO: 2 on the basis of the evidence of record in this matter. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. § 112, first paragraph.

In view of the foregoing remarks, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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FCE/sl
Attachment: Sequence alignment

ANNEX 1

Alignment between SEQ ID NOs. 2, 5 and 7 of application 10/570,122

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SEQIDNO:2       MSLGLLKFQAVGEEDEEDEEGESLDSVKALTAKLQLQTRRPSYLEWTAQVQSQAWRRAQA 60
SEQIDNO:5       ------------------------------------------------------------
SEQIDNO:7       ------------------------------------------------------------

SEQIDNO:2       KPGPGGPGDICGFDSMDSALEWLRRELREMQAQDRQLAGQLLRLRAQLHRLKMDQACHLH 120
SEQIDNO:5       ----------MDSALEWLRRELREMQAQDRQLAGQLLRLRAQLHRLKMDQACHLH 45
SEQIDNO:7       ----------IDSALEWLRRELREMQAQDRQLAGQLLRLRAQLHRLKMDQACHLH 45
                          :*********************************************

SEQIDNO:2       QELLDEAELELELEPGAGLALAPLLRHLGLTRMNISARRFTLC 163
SEQIDNO:5       QELLDEAELELELEPGAGLALAPLLRHLGLTRMNISARRFTLC 88
SEQIDNO:7       QELLDEAELELELEPGAGLALAPLLRHLGLTRMNISARRFTLC 88
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